

IN THE SPECIFICATION

Please insert at page 1, line 1, the following paragraph:

This application is a National Stage Application of International Application No. PCT/US2004/009572 filed March 26, 2004, which claims benefit of U.S. Provisional Application No. 60/458,079 filed March 27, 2003.

Please insert at page 16, line 21 the following new paragraphs:

In certain embodiments, the invention provides a method for identifying a compound that modulates animalia tRNA splicing endonuclease activity, said method comprising: expressing a nucleic acid comprising a reporter gene in a cell, wherein the reporter gene comprises a tRNA intron; contacting said cell with a member of a library of compounds; and detecting the expression of said reporter gene, wherein a compound that modulates tRNA splicing endonuclease activity is identified if the expression of said reporter gene in the presence of a compound is altered relative to the expression of said reporter gene in the absence of the compound or the presence of a control.

In certain embodiments, the invention provides a method of identifying an antiproliferative compound that inhibits animalia tRNA splicing endonuclease activity, said method comprising: microinjecting a substrate of a tRNA splicing endonuclease into a animalia cell, wherein the substrate is labeled at the 5' end with a fluorophore and at the 3' end with a quencher; contacting the cell with a member of a library of compounds; and measuring the activity of the tRNA splicing endonuclease, wherein an antiproliferative compound that inhibits tRNA splicing activity is identified if a fluorescent signal is not detectable or decreased in the presence of the compound relative to the absence of the compound or the presence of a control.

In certain embodiments, the invention provides a method of identifying an antiproliferative compound that inhibits animalia tRNA splicing endonuclease activity, said method comprising: transfecting a substrate of a tRNA splicing endonuclease into an animalia cell, wherein the substrate is labeled at the 5' end with a fluorophore and at the 3' end with a quencher; contacting the cell with a member of a library of compounds; and measuring the activity of the tRNA splicing endonuclease, wherein an antiproliferative compound that inhibits tRNA splicing activity is identified if a fluorescent signal is not detectable or decreased in the presence of the compound relative to the absence of the compound or the presence of a control.

In certain embodiments, the invention provides a method of identifying an antiproliferative compound that inhibits animalia tRNA splicing endonuclease activity, said

method comprising: microinjecting a substrate of a tRNA splicing endonuclease into a animalia cell, wherein said substrate is labeled at the 5' end with a fluorescent donor moiety and labeled at the 3' end with a fluorescent acceptor moiety; contacting the cell with a member of a library of compounds; and measuring the activity of the tRNA splicing endonuclease, wherein an antiproliferative compound that inhibits tRNA splicing activity is identified if the fluorescence emission of the fluorescent acceptor moiety at the wavelength of the fluorescent donor moiety in the presence of the compound is increased relative to the absence of the compound or the presence of a control.

In certain embodiments, the invention provides a method of identifying an antiproliferative compound that inhibits animalia tRNA splicing endonuclease activity, said method comprising: transfecting a substrate of a tRNA splicing endonuclease into a animalia cell, wherein said substrate is labeled at the 5' end with a fluorescent donor moiety and labeled at the 3' end with a fluorescent acceptor moiety; contacting the cell with a member of a library of compounds; and measuring the activity of the tRNA splicing endonuclease, wherein an antiproliferative compound that inhibits tRNA splicing activity is identified if the fluorescence emission of the fluorescent acceptor moiety at the wavelength of the fluorescent donor moiety in the presence of the compound is increased relative to the absence of the compound or the presence of a control.

In certain embodiments, the invention provides a method of preventing, treating, managing or ameliorating a proliferative disorder or a symptom thereof, said method comprising administering to a subject in need thereof a therapeutically or prophylactically effective amount of a compound, or a pharmaceutically acceptable salt thereof, identified according to a method of the invention.

In certain embodiments, the invention provides a method of preventing, treating, managing or ameliorating a proliferative disorder or a symptom thereof, said method comprising administering to a subject in need thereof an effective amount of a compound, or a pharmaceutically acceptable salt thereof, identified according to a method of the invention, wherein said effective amount decreases the activity of tRNA splicing endonuclease. In particular embodiment the proliferative disorder is cancer.

In certain embodiments, the invention provides a method of preventing, treating, managing or ameliorating a proliferative disorder or a symptom thereof, said method comprising administering to a subject in need thereof a therapeutically or prophylactically effective amount of an antiproliferative compound or a pharmaceutically acceptable salt thereof, identified according to a method of the invention.

In certain embodiments, the invention provides a method of preventing, treating, managing or ameliorating a proliferative disorder or a symptom thereof, said method comprising administering to a subject in need thereof an effective amount of an antiproliferative compound or a pharmaceutically acceptable salt thereof, identified according to a method of the invention, wherein said effective amount decreases the activity of tRNA splicing endonuclease. In particular embodiment the proliferative disorder is cancer.

In certain embodiments, the invention provides method for verifying the ability of a compound to inhibit animalia tRNA splicing endonuclease activity, said method comprising: expressing a nucleic acid comprising a reporter gene in a cell, wherein the reporter gene comprises a tRNA intron; contacting said cell with a compound; and detecting the expression of said reporter gene, wherein a compound that inhibits tRNA splicing endonuclease activity is verified if the expression of said reporter gene in the presence of a compound is reduced as compared to the expression of said reporter gene in the absence of said compound or the presence of a control.

In certain embodiments, the invention provides a method for verifying the ability of a compound to inhibit animalia tRNA splicing endonuclease activity, said method comprising: contacting a compound with a cell-free extract and a nucleic acid comprising a reporter gene, wherein the reporter gene comprises a tRNA intron; and detecting the expression of said reporter gene, wherein a compound that inhibits tRNA splicing endonuclease activity is verified if the expression of said reporter gene in the presence of a compound is reduced as compared to the expression of said reporter gene in the absence of said compound or the presence of a control.

In certain embodiments, the invention provides a method for verifying the ability of a compound to inhibit animalia tRNA splicing endonuclease activity, said method comprising: contacting a member of a library of compounds with a cell containing a nucleic acid comprising a reporter gene, wherein the reporter gene comprises a tRNA intron; and detecting the expression of said reporter gene, wherein a compound that inhibits tRNA splicing endonuclease activity is verified if the expression of said reporter gene in the presence of a compound is reduced as compared to the expression of said reporter gene in the absence of said compound or the presence of a control.